

# Criteria for Development of Animal Models of Diseases of the Gastrointestinal System

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THE CRITERIA for an acceptable model for gastrointestinal tract disease (Table 1) must involve: 1) an animal disease that closely mimics the human condition, 2) a host whose gastrointestinal tract resembles man in structure and function, and 3) availability, either as large numbers of a naturally occurring disease or as a reproducible experimental model. Inbred lines of rodents have long been exploited as models. Of the domesticated species, only the dog (and to lesser extent, the cat) has been sufficiently studied to understand the entire range of inflammatory, neoplastic, and inherited abnormalities that afflict the alimentary tract of man.

## Upper Digestive Tract

### Oropharynx

Three common conditions of the dog that await exploitation are oral papillomatosis,<sup>1</sup> malignant melanoma of the oral cavity, and dental bacterial plaque and its associated periodontal disease. Aged dogs are highly susceptible to plaque formation, and the bacterial species involved (actinomyces, streptococci, spirochetes, and veillonellae) closely resemble those of human plaque. Mechanisms of interbacterial adhesion are ecological determinants in the pathogenesis of plaque and should have relevance to models of lower tract disease. Experimental aggregation studies between actinomyces and streptococci have revealed bacterial surface interaction, ie, between glycoprotein receptors on one bacterial type and carbohydrates on the other. The "corn cob configuration" represents coccoid organisms closely adherent to filamentous bacteria (*Streptococcus sanguis* and *Bacterionemia matruchotii* in man).

Viral papillomatosis is common in the oral cavity of dogs and less so in swine, cattle, and rabbits. Bovine cutaneous papilloma (BCP) virus is of special interest because it stimulates both epithelial and connective tissue growth and is oncogenic in the hamster.<sup>2</sup> The known association of BCP virus and bracken fern toxin with proliferative bladder lesions (bovine enzootic hematuria) is now reflected in neoplastic disease of the alimentary

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From the National Animal Disease Center, Ames, Iowa.

Presented at the Workshop on Needs for New Animal Models of Human Disease, sponsored by the Registry of Comparative Pathology of the Armed Forces Institute of Pathology and the Universities Associated for Research and Education in Pathology, Inc., April 28-29, 1980, Washington, DC.

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Table 1—Outline of Animal Models of the Alimentary Tract

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I. Upper digestive tract
1. Oropharynx
2. Esophagus
3. Stomach
II. Intestine
1. Malabsorption and villous atrophy
2. Enterotoxins and hypersecretion
3. Enteroinvasive disease
4. Proliferative disease
5. Congenital megacolon
6. Colonic pigment lesions
III. Liver
1. Congenital metabolic disease
2. Hyperbilirubinemia
3. Hepatoencephalopathy
4. Chronic hepatitis
IV. Pancreas
1. Pancreatitis

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tract. There is a high incidence of alimentary tract cancer in beef cattle in British highlands (adjacent lowlands have low incidence). Papillomas and squamous cell carcinomas of the tongue, esophagus, and palate and adenocarcinoma of the intestine are associated with bracken fern ingestion, and tumors arise from preexisting virus-induced papillomas.<sup>3</sup> Of cattle with squamous cell carcinoma, 90% also had papillomas (some with direct evidence of papilloma-carcinoma conversion). In man, viral papillomas are problems of the larynx. In Japan and some European countries, bracken fern is marketed commercially for use in salads, and these preparations have been shown to be carcinogenic for rat bladder and intestine. Furthermore, milk from cows feeding on bracken fern is mutagenic for salmonellae in the Ames test. The carcinogenic substance in bracken fern has not been identified, but human consumption appears to increase the risk of esophageal cancer in man.

#### Esophagus

Esophageal achalasia is a disease of smooth muscle characterized by abnormal peristalsis, abnormal gastroesophageal sphincter function, and hypersensitivity of smooth muscle to stimuli. There are degenerative nerve lesions and abnormal cholinergic excitatory mechanisms to esophageal smooth muscle. There is anatomic evidence of abnormal dorsal motor nucleus of vagus, vagal nerves, and ganglion cells of Auerbach's myenteric plexus. Megaesophagus has been reported in animals with striated muscle esophagi (dog, mouse, rat, cow) and with striated/smooth muscle esophagi (cat, horse).

Congenital megaesophagus occurs in fox terriers and miniature schnau-

Table 2—Potential Animal Models for Gastric Disease

<b>Giant hypertrophic gastritis (Menetrier's disease)</b>	
Dog	Van Kruiningen: Vet Pathol 1977, 14:19
Mouse	Steward: J Natl Cancer Inst 1941, 1:489
Rhesus monkey	Lushbaugh: J Natl Cancer Inst 1947, 7:313
<b>Peptic ulcer</b>	
Swine	Muggenburg et al: Am J Vet Res 1964, 25:1673
Monkey	Natelson et al: Am J Diag Dis 1977, 22:888
Cat (mastocytoma)	Howard et al: Vet Pathol 1969, 6:146
<b>Gastric polyposis</b>	
Monkey (parasitosis)	Bonne and Sandground: Am J Cancer 1939, 37:183
<b>Amyloidosis</b>	
Dog	Cheville: Vet Pathol 1979, 16:292
<b>Carcinoma</b>	
Dog	Patnaik et al: Vet Pathol 1978, 16:600

zers.<sup>5</sup> In the latter, a colony has been bred for 9 years, and breeding ratios are compatible with a simple autosomal inheritance of 60% penetration of autosomal recessive modes of inheritance.<sup>6</sup>

#### Stomach

Peptic ulcer occurs in most animal species sporadically (most commonly in swine, cattle, and monkey), but a single ideal animal model for man has not been established. (See Table 2) In swine, 85% of lesions are in squamous epithelia of the gastric pars esophagia and 13% in the gastric body. The increasing incidence of gastric ulcer in swine has been loosely correlated with dietary changes and "stress," but experimental proof is lacking. Application of stress or serotonin-depleting factors probably enhances the incidence of gastric ulcer in most species. Unfortunately, most cases of animal gastric ulcer in most species. Unfortunately, most cases of animal gastric ulcers occur in complex terminal disease, eg, the high incidence found in NZB mice and uremic dogs.

In chronic uremia of dog and man, gastric lesions of edema, hemorrhage, and ulceration are responsible for the term "uremic gastritis."<sup>7</sup> Pathologic changes include expansion of the lamina propria, atrophy of gastric glands, and submucosal arteriopathy. In dogs, lesions are limited to the body and fundus. The lamina propria is markedly expanded by edema, mastocytosis, deposition of mucosubstances, fibroplasia, and mineralization. Muscular arteries have segmental lesions characterized by myocyte necrosis, calcification, and mucodegeneration. Mechanisms implicated in uremic gastric injury include activity of an uncharacterized small polypeptide toxin acting via adenyl cyclase in plasma membranes of glandular epithelial cells, ammonia generated by urea-splitting bacteria in gastric mucosa, and ischemia as a consequence of gastric vascular disease. Uremic gastropathy is a disease of mucosal lamina propria due to anoxia caused by diffuse vascular injury and to altered parietal cell function.

Zollinger-Ellison Syndrome of man involves recurrent peptic ulcers, gastric acid hypersecretion and non-beta-islet cell tumors of the pancreas. Tumor gastrin production leads to excessive gastric acid production and this, in turn, to ulceration. A similar syndrome in dogs is characterized by erosive esophagitis, parietal cell proliferation, intestinal villous atrophy, and thyroid C-cell hyperplasia. Most cases have thickened gastric mucosa and adrenocortical hyperplasia. Clinical signs include vomiting, diarrhea, anorexia, and weight loss. Gastrin extracted from canine pancreatic tumors is of Types II, III, IV, with high serum levels in some dogs.<sup>8</sup> Metastases of the pancreatic islet tumors occur, and pancreatic tumors have differing growth patterns (solid, trabecular, and acinar). This disease in dogs is rare. In 4 years, it occurred in 3/4174 autopsies in the Netherlands.

### Intestine

#### Malabsorption and Villous Atrophy

There is no widely available model for idiopathic villous atrophy of the small intestine, either for gluten enteropathy or for tropical sprue. Sporadic cases of intestinal malabsorption occur in dogs and horses but only in isolated cases. The most productive and available models for villous atrophy are the viral diseases of young animals.<sup>9</sup> (See Table 3.)

Mechanistically viral enteritis can be artificially placed into two classes: those affecting absorptive cells and those attacking crypt cells. Transmissible gastroenteritis (TGE) of piglets (coronavirus) is the prototype disease. TGE virus attacks and destroys differentiated villous absorptive cells, while crypt cells are spared. Marked villous atrophy leads to malabsorption and altered sodium, potassium, and chloride fluxes. After loss of infected columnar villous epithelial cells, the remaining immature villous epithelium is deficient in absorptive capacity. Rotaviruses that cause diarrheal disease in many species mimic TGE in pathogenesis. Cross-species infection has been shown experimentally with human, bovine, and porcine rotaviruses, but naturally occurring cross-species infection from animals to man has not been recognized.

In contrast to the above, parvoviruses (feline panleukopenia virus, mink enteritis virus) replicate in mitotically active epithelial cells lining the crypts of the Lieberkühn. Villous absorptive cells are not infected but they are not replaced as they slough from villi, and this lack of replacement leads to marked villous atrophy. Epithelium becomes flattened, and dilated crypt lumens are filled with cell debris and mucin.

#### Enterotoxins and Hypersecretion

Both *Escherichia coli* heat-labile toxin and the well-characterized enterotoxin of *Vibrio cholerae* cause hypersecretion of fluid and electrolytes

Table 3—Models of Viral Disease of the Intestine

<b>Rotavirus</b>	
Pig	Crouch et al: J Med Microbiol 1978, 11:325
Rabbit	Bryden et al: Vet Rec 1977, 99:323
Calf	Mebus and Newman: Am J Vet Res 1977, 38:553
Lamb	Snodgrass et al: Arch Virol 1967, 55:263
Mouse	Adams and Draft: Am J Pathol 1967, 51:39
Horse	
<b>Coronavirus</b>	
Pig (TGE)	Thake: Am J Pathol 1968, 53:149
Dog	Takeuchi et al: Lab Invest 1976, 34:539
Calf	Mebus et al: Am J Vet Res 1975, 36:1714
Mouse (MHV)	Broderson et al: Lab Anim Sci 1976, 26:824
Turkey (bluecomb)	Adams et al: J Comp Pathol 1972, 82:187
<b>Parvovirus</b>	
Dog	Hayes et al: J Am Vet Med Ass 1979, 174:1197
Cat	Carlson and Scott: Vet Pathol 1977, 14:173
Mink	Landsverk and Nordstoga: Acta Vet Scand 1978, 19:569
Calf	Storz et al: J Am Vet Med Ass 1978, 173:624
<b>Adenovirus</b>	
Wolf	Fletcher et al: J Am Vet Med Ass 1979, 175:897
Calf	Fujiwara and Konno: Natl Inst Anim Health Q 1968, 8:16
Monkey	Kim et al: J Infct Dis 1967, 117:292
Turkey	Cheville and Sato: Vet Pathol 1977, 14:567
<b>Paramyxovirus</b>	
Cow (BVD)	Meyling: Acta Vet Scand 1970, 11:59
<b>Enterovirus</b>	
Monkey (polio)	Kanamitsu et al: Jpn J Med Sci Biol 1967, 20:175
<b>Herpesvirus</b>	
Duck	Proctor: Vet Pathol 1975, 12:349

via activation of adenylyl cyclase and cAMP formation. Other microbial secretagogues that induce intestinal secretion by activation of adenylyl cyclase include the enterotoxin of *Salmonella typhimurium*, and *Shigella dysenteriae* toxin I. The effects of cAMP are mediated through activation of a protein kinase that phosphorylates a substrate responsible for the secretion of NaCl or NaHCO<sub>3</sub>. Classic models exist for both cholera toxin (primate) and *E coli* toxin (pig).<sup>10</sup>

#### Enteroinvasive Disease

In addition to causing toxigenic, cholera-like disease, some strains of *E. coli* produce dysentery-like infection. The *Shigella*-like *E. coli* actually penetrate and multiply in epithelial cells of the intestine. Rhesus monkeys have been used as human models for diarrheal diseases caused by enteroinvasive *E coli* and *Shigella dysenteriae*.

In addition to enterotoxigenic and enteroinvasive disease, *E coli* ap-

pears to cause illness by adherence to mucosal epithelium (without invasion or toxin elaboration). The model is a naturally occurring diarrheal syndrome in young rabbits characterized by superficial damage to the epithelial cell brush border with edema and inflammation of the lamina propria.<sup>11</sup>

#### Proliferative Disease

Crohn's disease (regional enteritis) is a segmental granulomatous enteritis of man of unknown cause. Lesions occur chiefly in the ileum, although most parts of the alimentary canal can be affected. The thickened, leathery intestine is nodular and may contain linear ulcers. Histologically, all layers of the intestine are infiltrated with lymphocytes, and plasma cells and granulomas with giant cells are common. Several models have been suggested for study of these chronic lesions including equine granulomatous enteritis, histiocytic colitis of Boxer dogs,<sup>12</sup> paratuberculosis of cattle (cause: *Mycobacterium pseudotuberculosis*), regional ileitis of swine, and proliferative ileitis of hamsters. Idiopathic regional enteritis of cocker spaniels might serve as a model, but the animals with this disease are not available in sufficient numbers.<sup>13</sup>

Proliferative ileitis of hamsters in an acute and chronic pyogranulomatous disease of the ileum with marked proliferation of epithelium and herniation of crypts into the serosa. Animals suffer severe diarrhea, dehydration, and emaciation. The initial lesion is epithelial hyperplasia of the ileal mucosa and is followed by severe inflammatory changes. Secondary stromal hyperplasia leads to markedly thickened ileal mucosa and stenosis of the intestinal lumen. Inflammation of the wall permits mucosa to protrude through the weakened muscle fibers to form false diverticulae under the serosa. Peritonitis due to rupture of the subserosal diverticula is common.<sup>14</sup> The cause of the initial ileal hyperplasia is not known.

Equine granulomatous enteritis<sup>15</sup> is also a segmental enteritis of unknown cause. Horses with this disease are emaciated and have fibrous plaques and granulomatous nodules over intestinal serosa, chiefly in the ileum. The cellular infiltrates consist of lymphocytes and macrophages and occasional plasmacytes and giant cells. Villous atrophy may be marked in the small intestine. Edema of the lamina propria and submucosa is found in most cases. Bacterial and fungal stains are negative, and attempts to transmit the disease (with cell-free tissue suspensions) to rabbits and horses have failed.

Proliferative enteropathy of swine caused by *Campylobacter sputorum* subsp. *mucosalis* is characterized by bacteria in the apical cytoplasm of epithelial cells in adenomatous areas.<sup>16</sup> Glands of affected intestine are

composed of immature epithelium, and cells are deficient in enzymes normally found in mature absorptive cells.<sup>17</sup>

#### Congenital Megacolon

Aganglionic megacolon occurs in piebald-lethal and lethal-spotting strains of mice. Their phenotype can be controlled by selective breeding, and they are valuable models for neural crest defects and defects in form and function of the enteric nervous system. The general characteristics of the disease have marked resemblance to Hirschsprung's disease of man.<sup>18,19</sup>

#### Colonic Pigment Lesions

Two types of lipofuscin accumulation occur in the colon of man, and both are found in the intestines of aged dogs. The brown bowel syndrome is a symptomless process characterized by aggregates of pigment-laden macrophages in the mucosal connective tissues. It is associated with prolonged use of anthraquinone purgatives. In melanosis coli, large collections of lipofuscin granules develop in the smooth muscle cells of the muscular layers. These changes are seen in protein-losing enteropathies, chronic malabsorption, and chronic pancreatitis.

#### Liver

##### Congenital Metabolic Disease

Round heart disease of inbred small white turkeys is characterized by severe cardiac dilatation and large PAS-staining diastase-resistant cytoplasmic inclusions in hepatocytes. Affected turkeys have low total plasma protein and low plasma trypsin inhibitory capacity and have been presented as a model for  $\alpha_1$ -antitrypsin deficiency of man.<sup>20</sup> Furazolidone produces primary hepatic damage in turkeys, reflected in lowered protein and trypsin inhibitory capacity, and alterations are superimposed on round heart disease in inbred flocks. Although the inclusions have been reported to be lysosomes, it is my suggestion that they represent peroxisomes. Peroxisome deficiency is also said to be the basis of cerebrohepatorenal syndrome (Zellweger) of children with facial deformities, retardation, hepatomegaly, and central nervous system malformations.<sup>21</sup>

#### Hyperbilirubinemia

Newborn babies develop hyperbilirubinemia because the hepatic system for conjugating and excreting bilirubin is functionally immature at birth. Bilirubin accumulates in the circulation and extravascular tissues

until the excretory apparatus becomes functional, usually within the first week after birth. When prolonged, circulating bilirubin diffuses into the brain where it exerts a toxic effect. Gunn rats serve as a model for this transient hyperbilirubinemia, for they are congenitally unable to conjugate bilirubin and have lifelong hyperbilirubinemia. Their bile contains no conjugated bilirubin and only a low concentration of unconjugated bilirubin. What human newborns have for only a brief span, homozygous Gunn rats have all their lives. Gunn rats have been effectively used in models of phototherapy where blue light converts bilirubin to isomers that are transported in blood and excreted in bile. They respond by bleaching the skin, subsidence of plasma bilirubin levels and prompt excretion of pigment in bile.

#### Hepatoencephalopathy

Hepatoencephalopathy is being recognized with increasing frequency in dogs. Causes include anomalous portal venous circulation, severe hepatocyte damage with reduced detoxification, and congenital deficiency of urea cycle enzymes.<sup>22</sup> The most important toxic substance implicated is ammonia, although mercaptans, short-chain fatty acids, indoles, biogenic amines, and certain amino acids have been suggested. Hepatocyte atrophy appears to be due to diversion of endogenous insulin from the liver. Portacaval shunt surgery has been used in man for treatment of familial hypercholesterolemia. Dogs and swine have been used in surgical studies and show similar reductions in plasma cholesterol.<sup>23</sup>

#### Chronic Hepatitis

Several rodent models for chronic hepatic disease exist, including reoviruses, murine hepatitis virus (coronavirus), and woodchuck hepatitis, which resembles infectious hepatitis of man. A transmissible disease involving hepatic necrosis also occurs in horses. Canine adenovirus 1, the cause of infectious canine hepatitis, produces acute liver necrosis and severe systemic infection. Dogs dying of fulminating disease usually do not develop detectable antibodies; those that recover have high antibody titers and are solidly immune to reinfection. Dogs with incomplete immunity may develop chronic progressive hepatic injury.<sup>24</sup> Foci of liver degeneration are accompanied by infiltration of plasma cells and monocytes in the sinusoids and triads. Fibrosis is a late sequela. Viral antigens cannot be detected by fluorescent antibody techniques, and the role of canine adenovirus remains vague.

### Pancreas

Three potential models of exocrine pancreatic disease occur in the dog: pancreatitis, acinar cell carcinoma,<sup>25</sup> and juvenile atrophy.<sup>26</sup> Spontaneous juvenile atrophy shows breed disposition, absence of ductal damage or fibrosis, and retention of islets. Studies on a similar model in CBA/J mice indicate that acinar cell "autodigestion" is the mechanism of cell death.<sup>27</sup>

### Pancreatitis

Acute pancreatitis has been reported in dogs, cats, mice, cattle, swine, and fish. Only in dogs does it occur commonly enough to serve as spontaneous model. Factors associated with onset include obesity, fatty meals, and hyperlipidemia. Affected dogs, like humans, show marked glucose intolerance, and elevated serum amylase and lipase have the same diagnostic significance as in humans. The critical early lesion appears to occur at termini of pancreatic ductules. Lesions of marked cell swelling and fatty degeneration of centroacinar cells, in our material, seem to precede necrosis of exocrine parenchymal cells.

Dogs also suffer chronic relapsing pancreatitis, and diabetes mellitus develops in over half of these animals. Chronic lesions of ductal dilatation and ductal and parenchymal calcification that characterize human chronic pancreatitis are rarely seen in dogs.

Since the days of Flexner and Opie, dogs have been used for the majority of studies on pancreatitis. Increased ductal pressure is an assumed cause, and models use ductal ligation with intravenous secretin or retrograde infusions into the ductal system. Investigators must be aware that normal serum amylase levels are higher in dogs than in man, that the canine small intestine is an active amylase-secreting organ, and that canine liver degrades amylase more slowly than that of man.

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